A Quantitative Risk Assessment of the Human Health Impacts Due to Macrolide Use in Swine

Hurd HS*, Malladi S

Food Risk Modeling and Policy Lab, College of Veterinary Medicine, Iowa State University, Ames, Iowa, USA
*Corresponding author: shurd@iastate.edu

Abstract
We used a retrospective modeling approach instead of the traditional farm to fork model; back calculating (C_m) the number of human macrolide resistant C. *coli* infections caused by eating contaminated pork, due to specific macrolide use in swine. We used the estimated number of culture confirmed human infections (C_t). As a measure of human health risk, we then calculated the expected number among the (C_m) cases that experience an adverse treatment outcome (prolonged illness) due to macrolide resistance, using estimates for fluoroquinolone. We divided the model into Release, Exposure and Consequence assessment sections according to FDA guidance 152 and utilized @Risk software with 20,000 iterations for simulation. The results show the human health risks are negligible. For example, the predicted annual risk, for prevention and growth promotion uses is only 1 in 92 million per U.S. resident, with a 5% chance it could be as high as 1 in 52 million. Our model focuses on the impact of resistance on human treatment. It assumes that macrolide resistance *C. coli* infection reduces treatment efficacy. However, it is possible that risks less than our estimates.

Introduction
Campylobacter is considered an important food-borne pathogen. Erythromycin, a macrolide antibiotic, is recommended for the treatment and control of severe culture confirmed campylobacteriosis. Recent studies have reported higher frequencies of resistant Campylobacter in conventional swine farms compared to antibiotic free farms. There are concerns that macrolide antibiotic use on swine farms may increase human health risk. Our objective was to conduct a stochastic quantitative risk assessment of potential adverse health outcomes due to macrolide resistant *C. coli* infection originating from macrolide use on the swine farm.

Materials and Methods
We chose a retrospective modeling approach instead of the traditional farm to fork model which is significantly more data intensive. Hence, we back calculated (C_m) the number of human macrolide resistant C. *coli* infections caused by eating contaminated pork, due to a specific type of macrolide use in swine. We started with estimated number of total culture confirmed human infections (C_t). As a measure of human health risk, we then calculated the expected number among the C_m cases that might experience an adverse treatment outcome due to macrolide resistance. An adverse treatment outcome refers to ineffective treatment resulting in prolonged illness such as extra days of diarrhea or fever. We divided our model into Release, Exposure and Consequence assessment sections according to FDA guidance 152 (www.fda.gov/cvm/guidance/fguide152.DOC). We utilized a variety of uncertainty distributions for the parameters and simulated with @Risk software (20,000 iterations).

Release Assessment: In this section, we calculated the fraction of *C. coli* population in swine that is macrolide resistant due to different types of macrolide (r_m). Following we describe the estimation of r_m for prevention and growth promotion uses (Tylan Premix® and Tylan Sulfa-G ®) followed by the estimation for treatment and control uses (Tylan Injection®, Tylan Soluble® and Pulmotil Premix®)

Let r_b be the background resistant fraction that exists without exposure to macrolide, and r_f be the steady state resistant fraction in a conventional farm in which a fraction (α) of the swine have been exposed to a specific macrolide. The total resistant fraction (r_f) is linearly related to the fraction exposed (α) as a first order approximation shown in Equation 1.

$$r_t = r_b + \alpha(1 - r_b)p \quad (1)$$

Where, the constant *(p)* corresponds to the probability that a bacterium among the fraction $\alpha(1-r_b)$ of the C. *coli* population that is susceptible, acquires resistance or is replaced by a resistant bacterium. The term $\alpha(1-r_b)p$ is equal to (r_m), the fraction resistant due to macrolide use.

To estimate *p*, we used the difference in the resistant fractions between antibiotic free (ABF) farms and conventional farms (using macrolide). Two studies reported 38% of 745 C. *coli* isolates from ABF farms and 77% of 347 C. *coli* isolates from conventional farms (r_t) were resistant (Gebreyes et al., 2005 and Thakur and Gebreyes 2005). Hence, we estimated r_b = 38% and r_t = 77% (Mean of the Beta distributions in Table 2). We assumed that all the animals in the conventional farms were exposed to macrolide i.e. α =1. By solving Equation 1, we calculated *p* = 62% for prevention and growth promotion uses. From industrial usage data, the overall national fraction of swine exposed for prevention and growth promotion uses was 58% (Doane, 2005). Finally, we computed, r_m=21% (resistance in C. *coli* in swine that is due to macrolide use).

For estimation of *p* due to treatment uses, we had to use data on *Enterococci spp.* Jackson et al., 2004 found that the resistant fraction in *Enterococci spp.* from farms that used macrolide for prevention alone was twice of that in farms with treatment uses. Therefore, we assumed (p) for treatment uses is 31% or half of the (*p*) for prevention or growth promotion uses.

Exposure assessment: For the Exposure assessment, we estimated the number of culture-confirmed human C. *coli* infections that are resistant due to macrolide use in swine (C_m) utilizing Equation 2.

$$C_m = C_t \eta\, r_m \quad (2)$$

Where, the population etiologic fraction (η) is defined as the fraction of human infections caused by C. *coli* from swine. Total number of culture confirmed human C. *coli* infections per year is C_t.

To calculate the etiologic fraction (η) for swine, we conservatively (Risk increasing) assumed that all the C. *coli* infections (C_t) are caused by eating only chicken or pork, then distributed the cases according to relative carcass contamination rates. Table 1 provides the data sources, and the estimated values of the parameters utilized in calculating η. To estimate the kilograms of contaminated pork, we assumed that all ground pork from a contaminated swine carcass is contaminated, while the non ground pork is not. For kilograms of contaminated chicken we assumed all servings from a contaminated carcass were contaminated. As a result, we calculated that 12.4% of the human C. *coli* infections are caused from swine.

Table 1 Estimation of etiologic fraction for *C. coli* for swine and chicken

Parameter Details	Chicken	Swine
Carcass contamination rate of *Campylobacter* spp (Food safety and Inspection service 1994)	88% Beta(1149, 190)	32% Beta(666,1448)
Fraction of C.*coli* among *Campylobacter* spp isolates (NARMS: National Antimicrobial Resistance Monitoring System retail 2002-2003)	30% Beta(231,527)	1 (assumption)
Fraction of carcasses contaminated with C.*coli*	27%	32%
Expected Fraction of swine carcass processed into ground meat (Hurd et al., 2004)	100%	21%
Overall fraction C.*coli* contaminated meat servings after slaughter	27%	6.72%
Annual kilograms of meat produced (National Agricultural Statistics Service, 2006)	16 billion	9.3 billion
Annual kilograms of C. *coli* contaminated servings	4.4 billion	0.620 Billion
Etiologic fractions for C. *coli* from chicken and swine	87.6%(86-89)%	12.4(11 -14)%

Consequence assessment: We calculated the annual number of adverse outcomes due to macrolide use (C_{ao}) according to Equation 3. Where τ is the joint probability that a culture confirmed infection is treated with an antibiotic and the prescribed antibiotic is macrolide. The parameter, ρ, is the probability that adverse outcome occurs due to macrolide resistance.

$$C_{ao} = C_m \rho \tau \quad (3)$$

We are unaware of any evidence that macrolide resistant *Campylobacter* causes any more illness days than susceptible or that erythromycin treatment has any clinical benefit, i.e. ρ is likely zero. However, to be conservative, we utilized fluoroquinolone data to estimate ρ; erroneously assuming that macrolide and fluoroquinolone resistant infections have identical clinical consequences.

Table 2 Parameter estimates and risk assessment of adverse treatment outcomes to *C.coli* infections that are resistant due to macrolide use in swine

Parameter	Prevention and Growth promotion	Treatment	All uses	Data sources
Release Assessment				
α, Fraction of animals exposed to macrolide	58%	17.3%		Doane marketing survey (2005)
r_b, Background resistance	38% Beta(229,518)*	--		Gebreyes et al., (2005);Thakur and Gebreyes (2005)
r_t, Resistant fraction in farms utilizing macrolide	r_t=77% Beta(12,823)*	--		
P, Probability of resistance development	62%	31.2%		
r_m, Fraction resistant due to macrolide use	21%	3.3%		
Exposure Assessment				
Annual number of *Campylobacter spp* cases (culture-confirmed)	38,315 Gamma(5665,1)6.76*			Foodnet 2004
Fraction of human *Campylobacter* cases caused by C. *coli*	4.3% Beta (64,1409)*			Gupta et al., 2004
C_t, *Annual number of C. coli cases*	1647			
η, Etiologic fraction	12.40%			
C_m, *number of cases resistant due to macrolide use/year*	46	7	53.0	
Consequence Assessment				
τ Probability that a culture confirmed case is treated with a macrolide	32% Beta(320,501)Beta(938,193)*			Nelson et al., 2004
ρ Probability of an adverse outcome given macrolide resistance	22% Beta(7,24)*			Kushner et al., 1995; Sanders et al., 2002
C_{ao} *Annual number of adverse outcomes* (median)	3.23 (1.61-5.65)	0.5(0.23-0.84)	3.7 (1.8-6.4)	
Annual risk of an adverse outcome for a person in the US (median)	1 in 92 (52-184) million	1 in 620(354-1250) million	1 in 80 (45-162) million	

Confidence intervals provided are two sided at 90% confidence. The human health consequences are given as medians. Annual risk was calculated as the ratio of the US population of 298 million/C_{ao}. * These are uncertainty distributions for the parameter estimates which were simulated using @Risk® software.

Results

The parameter estimates, their distributions, data sources, the results for the risk assessment are summarized in Table 2. The median risk of an adverse treatment outcome due to macrolide use induced resistance in C. *coli* from swine is less than 1 in 80 million. The risk is less than 1 in 45 million with 95%. The risk due to treatment uses is negligible and is less than 1 in 354 million with 95% confidence.

Discussion

Our results show that at worst, the human health risk due to macrolide induced resistance in C. *coli* from swine is very low even with the conservative assumptions we made. Reasons for the low risk include the low fraction of human infections caused by C. *coli* and the relatively higher *C. coli* contamination rate of chicken carcass. Furthermore, the risk due to treatment uses is negligible as only a very small fraction of swine is exposed to it. We had to make very conservative assumptions such as that all the *C. coli* infections are caused from chicken or swine due to the lack of data on the etiologic fraction. More data on the etiologic fraction and the clinical consequences of erythromycin resistance is required. In addition, Sensitivity analysis showed that the fraction of human infections caused by *C. coli* and macrolide resistant fractions in conventional and ABF farms are other parameters leading to a significant uncertainty in the resulting risk estimates, demonstrating the need for further research in this area.

References

DOANE MARKETING RESEARCH (2005). "Doane Marketing Research Animal Health Market Study (2003-2005)".

GEBREYES, W., A., et al., 2005. Campylobacter coli: prevalence and antimicrobial resistance in antimicrobial-free (ABF) swine production systems. *Journal of Antimicrobial Chemotherapy,* 56(4), 765-768.

GUPTA, A., et al., 2004. Antimicrobial resistance among Campylobacter strains, United States, 1997-2001. *Emerging Infectious Diseases,* 10(6), 1102-1109.

HURD, H. S., et al., 2004. Public health consequences of macrolide use in food animals: a deterministic risk assessment. *Journal of food Protection*, 67(5), 980-992.

JACKSON C.R, et al., 2004. Effects of Tylosin use on erythromycin resistance in enterococci isolated from swine. *Applied Environmental Microbiology,* 70:4205-10.

KUSCHNER, R. A., et al., 1995. Use of azithromycin for the treatment of Campylobacter enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. *Clinical Infectious Diseases*, 21(3), 536-541.

NELSON, J. M., et al., 2004. Prolonged diarrhea due to ciprofloxacin-resistant campylobacter infection. *Journal of Infectious Diseases* 190(6), 1150-1157.

THAKUR, S. AND GEBREYES, W. A. (2005). Prevalence and antimicrobial resistance of Campylobacter in antimicrobial-free and conventional pig production systems. *Journal of Food Protection*, 68(11), 2402-2410.

SANDERS, J. W., et al., 2002. An observational clinic-based study of diarrheal illness in deployed United States military personnel in Thailand: presentation and outcome of Campylobacter infection. *American Journal Tropical Medicine and Hygiene*, 67(5), 533-538.